Saudi Journal of Ophthalmology (2011) **25**, 395–404

King Saud University

Saudi Journal of Ophthalmology

www.saudiophthaljournal.com
www.ksu.edu.sa
www.sciencedirect.com

GLAUCOMA UPDATE

Mitochondrial DNA abnormalities in ophthalmological disease

Grainne S. Gorman, MRCP; Robert W. Taylor, PhD, FRCPath *

Mitochondrial Research Group, Institute for Ageing and Health, Newcastle University, United Kingdom

Received 31 January 2011; revised 7 February 2011; accepted 12 February 2011
Available online 18 February 2011

KEYWORDS

mtDNA;
Mitochondrial disease;
Progressive external ophthalmoplegia;
Optic atrophy;
LHON;
Retinopathy;
Extraocular muscle

Abstract Mitochondrial disorders are a group of clinically heterogeneous diseases, commonly defined by lack of cellular energy due to genetic defects of oxidative phosphorylation (OXPHOS). Ocular involvement is a prominent clinical feature of mitochondrial disease. This can manifest as optic nerve dysfunction specifically involving retinal ganglion cells as typified by Leber hereditary optic neuropathy (LHON), or progressive external ophthalmoplegia (PEO) and ptosis involving the extraocular muscles which is commonly associated with either primary mitochondrial DNA (mtDNA) mutations or acquired mtDNA defects secondary to a nuclear genetic disorder of mtDNA maintenance. In this short review, we will outline the unique characteristics of mitochondrial genetic disease and its investigation with reference to the clinical features and molecular genetic abnormalities underlying mitochondrial ophthalmological disease.

* Corresponding author. Address: Mitochondrial Research Group, Institute for Ageing and Health, The Medical School, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, United Kingdom. Tel.: +44 (0) 191 2223685; fax: +44 (0) 191 2824373.
E-mail address: r.w.taylor@ncl.ac.uk (R.W. Taylor).

Peer review under responsibility of King Saud University.
doi:10.1016/j.sjopt.2011.02.002

Production and hosting by Elsevier

Contents

1. Introduction

Mitochondrial diseases are a clinically multifarious group of genetic disorders that affect organs heavily dependent on aerobic metabolism with extensive phenotypic and disease burden variability (McFarland et al., 2010). Neuro-ophthalmic manifestations of mitochondrial disorders are common and include retinal, macular and optic nerve dysfunctions, external ophthalmoplegia with ptosis and retrochiasmal visual loss. Ocular features are rarely in isolation and may be associated with neurological and/or systemic symptoms. The differential diagnosis of ocular muscle dysmotility is broad and includes ocular myasthenia, ocular myositis, thyroid associated orbitopathy, congenital cranial dysinnervation disorders, oculopharyngeal muscular dystrophy and other neurodegenerative or dystrophic disorders (Schoser and Pongratz, 2006). This review article highlights the salient clinical and molecular features of ocular manifestations of mitochondrial diseases.

1.1. Basic mitochondrial genetics

Mitochondria are responsible for producing >90% of a cell's ATP through the pathways of electron transfer and oxidative phosphorylation (OXPHOS) that comprise the respiratory chain. The only location of extrachromosomal DNA within the cell, mitochondria are under the dual genetic control of both nuclear DNA and the mitochondrial genome (mtDNA), a small (16.6 kb) multicopy, double-stranded circular DNA molecule which encodes 13 essential polypeptides of the respiratory chain and the necessary RNA machinery for their translation (Fig. 1). The remaining protein subunits that make up the respiratory chain complexes, together with many hundreds of other proteins found within the organelle – many of which are required for mtDNA maintenance, replication and the translation of mitochondrial proteins – are synthesised on cytoplasmic ribosomes and specifically targeted and sorted to their correct mitochondrial location.

The mitochondrial genome possesses unique characteristics that distinguish it from Mendelian genetic rules (Taylor and Turnbull, 2005). It is strictly maternally-inherited, and is polyploid, i.e. multiple copies of mtDNA are present within each mitochondrion with several thousands present in individual cells. Normally, all of the mitochondrial genomes within an individual are identical, a situation termed *homoplasmy*. However, a mutation occurring in one copy of mtDNA can eventually lead to dual populations of wild type and mutated mtDNA coexisting within the same cell – *heteroplasmy*. At mitosis, both wild-type and mutated mtDNA are randomly segregated to each daughter cell, thereby affecting both disease expression and inheritance, further contributing to the wide range of clinical presentations seen in mtDNA disorders. The majority of deleterious mtDNA mutations are heteroplasmic, with clinical manifestations only becoming evident when the number of mutated mtDNA molecules exceeds a critical 'threshold'. This threshold varies between organs depending upon their energy requirements, and reflects the incapacity of the remaining wild type mtDNA to compensate for the mutated mtDNA, leading to OXPHOS impairment and consequently cellular (routinely demonstrated by the histocytochemical assessment of cytochrome *c* oxidase (COX) activity) and organ dysfunction (see later). Although many important factors such as nuclear genetic background and mtDNA genotype can influence the phenotypic effect of particular mtDNA mutations, the relative abundance and specific tissue distribution of mutated mtDNAs are key determinants of the severity of the resulting clinical phenotype.

1.2. The laboratory diagnosis of mitochondrial disease

The laboratory diagnosis of mitochondrial disease is far from straightforward; mtDNA heteroplasmy, the lack of clear geno-